REMARKS

Claims 1-57 and 62-63 were pending. Claims 6, 7, 15 and 44 have been canceled. Support for the amendment to claims 1, 54 and 57 may be found, inter alia, in originally filed claim 7 and on page 17, lines 3-6 of the specification. Support for new claims 64-69 may be found, inter alia, as follows: claim 64, on page 11, lines 12-14; claim 65, on page 17, lines 3-17; claim 66, on page 17, lines 3-17; claim 67, line page 11, lines 18-22; claim 68, on page 22, lines 18-19; claim 69, in original claim 21. Withdrawn claim 48 has been redrafted as an independent incorporating all the elements of its parent claim 44, not canceled. This amendment does not add any new matter. All new claims read on the elected invention and species. Entry of this amendment is requested such that claim 1-5, 8-14, 16-43, 45-57 and 62-69 will be pending.

Restriction Requirement

The Examiner states that the claims are been examined to the extent that they read on the following elected species:

(1) "Allogeneic" for the relationship of the EGC's to the subject.

(2) "Hemangioblasts" as the endothelial generating cells;

(3) "Bone Marrow" as the source of MSCs.

(4) "Autologous" for the relationship of the MSCs to the subject.

(5) "Myocardial Ischemia" as the disorder

(6) "Not modified by exogenous DNA" as the genetic state of the EGCs.

(7) "VEGF" as the polypeptide being co-administered.

Claim Objections

The Examiner objects to claim 12 because a space should be inserted before the word "VE-cadherin" at line 2. In response, Applicants have amended claim 12 to obviate this ground of rejection

The Examiner objects to claim 63 because the claim should read "are administered" at line 2. In response, Applicants have amended claim 63 to obviate this ground of rejection.

Rejections under 35 U.S.C. § 112, 2nd Paragraph, Clarity

Claims 3, 8, and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The Examiner alleges that claim 8 is unclear due to the recitation of "endothelial cell-promoting culture condition." In response, Applicants have amended claim 8 to clarify the claimed subject matter. Applicants also note that the specification provides cell culture conditions that result in the differentiation of an endothelial generating cell into an endothelial cell, such as those in paragraph 69.

The Examiner alleges that claims 3 and 15 are identical and that one of them should be canceled. In response, applicants have canceled claim 15.

The Examiner also alleges that claims 2 and 16 are identical and that one of them should be canceled. Applicants note that claim 16 recites more elements that claims 2 and therefore the two claims are of different scope. While claim 16 recites that the endothelial generating cells may be endothelial progenitor cells, hemangioblasts or hematopoietic stem cells (or a combination thereof), claim 2 recites only that they may be hemangioblasts. Since claim 2 does not recite endothelial progenitor cells or hematopoietic stem cells, it has a different scope that claim 2. Reconsideration and withdrawal of this ground of rejection is requested.

Rejections under 35 U.S.C. § 102(a) - Ueno

The Examiner rejects claims 1-4, 6-8, 11-17, 19-21, 23-28, 32-36, 40-47, and 49-57 under 35 U.S.C. 102(a) as being allegedly anticipated by Ueno et al. (U.S. Pat. Pub. 2002/0037278), taken in light of Yin et al. and Haynesworth. The Examiner alleges that Ueno teaches the administration of bone-marrow derived MNCs to a subject, and that MNCs contain both EGCs and MSCs. The Examiner concludes that Ueno inherently teaches the administration of these two cell populations to treat ischemia.

Applicants traverse this ground of rejection. Independent claims 1, 54 and 57 have been amended to recite "wherein the [cells] are enriched from bone marrow mononuclear cells at least

two-fold prior to administration to the subject." Ueno does not teach the enrichment of any cell type from MNCs, such as by removing non-EGCs from the MNC population. While Ueno at best may teach the isolation of MNCs from crude bone marrow, it fails to teach the subsequent enrichment of any cell type, let alone by at least two-fold from this MNC population. Since Ueno fails to teach this element of claims 1, 54 and 57, it cannot anticipate these claim nor their dependent claims.

In addition to failing to teach or suggest all the elements of claim 1, Ueno fails to teach or suggest elements of many of the dependent claims.

Ueno, for example, fails to teach the administration of 1×10^4 human endothelial generating cells as recited in claims 25, or of between 1×10^4 to 5×10^8 human endothelial generating cells as recited in claim 26. Ueno fails not only to teach the administration of these amounts of EGCs, it also fails to teach the administration of these amounts of hemangioblasts, which are the elected species of EGCs.

Ueno also fails to teach the administration of human EGCs and MSCs in a ratio of from about 5:1 to about 1:5 as recited in claims 28 and 53. And it also fails to teach this same ratio but of human *hemangioblasts* to MSCs. The Examiner has failed to identify how these ratios are allegedly taught or suggested by Ueno.

Ueno also fails to teach the intracoronary injection of cells, as recited in claims 33 and 63. In fact, Applicants were unable to find the tern "intracoronary" anywhere in Ueno.

Ueno also fails to teach the elements of amended claim 20. Claim 20 recites the use of "culture expanded" MSCs. Ueno does not teach the culturing of any cell type, let alone of MSCs.

Ueno also fails to teach the elements of the new claims.

For example, Ueno fails to teach the administration of between 10^4 to 5×10^8 mesenchymal stem cells as recited in claim 64. The Examiner alleges that Ueno teaches the administration of 6.9×10^6 BM-MNCs to the subject. However, 6.9×10^6 BM-MNC would contain, at best, only from 6.9 to 690 MSCs because the instant specification teaches that human MSC are very rare, "comprising about 0.01-0.0001% of the total nucleated cells of bone marrow." (page 19, lines 9-10). The methods of Ueno, then, result in the administration of far fewer MSCs within the MNC population that those recited in claim 64. Ueno then fails to anticipate claim 64.

Similarly, Ueno fails to teach the use of EGCs that have been enriched from mononuclear cells as recited in claim 65, and specifically via immunoselection as recited in claim 66. Ueno does not teach the isolation of *any* cell type from a population of mononuclear cells.

Applicants request that if the Examiner should maintain the rejection over Ueno, that she specifically identify how Ueno allegedly teaches or suggest each element of any rejected claim.

Rejections under 35 U.S.C. § 102(e) - Ueno

Claims 1-4, 6-8, 11-17, 19-21, 23-28, 32-36, 40-47, and 49-57 are also rejected under 35 U.S.C. 102(e) as being anticipated by Ueno et al., taken in light of Yin et al., and Haynesworth.

Applicants traverse this ground of rejection. Ueno fails to anticipate these claims for all the reasons stated in the preceding section.

Rejections under 35 U.S.C. § 102(a) - Tateishi-Yuyama

Claims 1-4, 6-7, 11-17, 20-21, 23-28, 32-33-46 and 50-57 are rejected under 35 U.S.C. 102(a) as being allegedly anticipated by Tateishi-Yuyama et al. ("Tateishi"), taken in light of Ueno et al., Haynesworth and Yin et al.

Applicants traverse this ground of rejection. Independent claims 1, 54 and 57 have been amended to recite "wherein the [cells] are enriched from bone marrow mononuclear cells at least two-fold prior to administration to the subject." Tateishi does not teach the enrichment of any cell type from MNCs, such as by removing non-EGCs from the MNC population. While Tateishi at best may teach the isolation of MNCs from crude bone marrow, it fails to teach the subsequent enrichment of any cell type, let alone by at least two-fold from this MNC population. Since Tateishi fails to teach this element of claims 1, 54 and 57, it cannot anticipate these claim nor their dependent claims.

In addition to failing to teach or suggest all the elements of claim 1, Tateishi fails to teach or suggest elements of many of the dependent claims.

Tateishi, for example, fails to teach the administration of 1×10^4 human endothelial generating cells as recited in claims 25, or of between 1×10^4 to 5×10^8 human endothelial

generating cells as recited in claim 26. Tateishi fails not only to teach the administration of these amounts of EGCs, it also fails to teach the administration of these amounts of hemangioblasts, which are the elected species of EGCs.

Tateishi also fails to teach the administration of human EGCs and MSCs in a ratio of from about 5:1 to about 1:5 as recited in claims 28 and 53. And it also fails to teach this same ratio but of human *hemangioblasts* to MSCs. The Examiner has failed to identify how these ratios are allegedly taught or suggested by Tateishi.

Tateishi also fails to teach the intracoronary injection of cells, as recited in claims 33 and 63. In fact, Applicants were unable to find the tern "intracoronary" anywhere in Tateishi.

Tateishi also fails to teach the elements of amended claim 20. Claim 20 recites the use of "culture expanded" MSCs. Tateishi does not teach the culturing of any cell type, let alone of MSCs.

Tateishi also fails to teach the elements of new claims 65 and 66. Tateishi fails to teach the use of EGCs that have been enriched from mononuclear cells as recited in claim 65, and it fails to teach the isolation of mononuclear cells via immunoselection as recited in claim 66. Tateishi does not teach the isolation of *any* cell type from a population of MNCs.

Claims 50 recites infusion of the cells "into at least one coronary artery." Claim 52 further defines the coronary artery as "an epicardial vessel that provides collateral blood flow to said ischemic myocardium in the distribution of a chronic totally occluded vessel." Tateishi relates to limb ischemia, not to cardiac ischemia. Tateishi fails to teach or suggest the administration of cells into a coronary artery, and therefore cannot anticipate claims 50 and 52.

Similarly, claims 51 recites that that the ischemic myocardium "comprises an area of viable myocardium." Tateishi relates to limb ischemia, not to myocardial ischemia. Because Tateishi fails to teach or suggest "an area of viable myocardium" it cannot anticipate claim 51.

Applicants request that if the Examiner should maintain the rejection over Tateishi, that she specifically identify how Tateishi allegedly teaches or suggest each element of any rejected dependent claim.

Rejections under 35 U.S.C. § 102(a) - Strauer

Claims 1-4, 6-8, 11-17, 19-21, 23-28, 32-34, 36-47, and 49-57 are rejected under 35 U.S.C. 102(a) as being anticipated by Strauer et al., taken in light of Ueno et al., Haynesworth, and Yin et al.

Applicants traverse this ground of rejection. Independent claims 1, 54 and 57 have been amended to recite "wherein the [cells] are enriched from bone marrow mononuclear cells at least two-fold prior to administration to the subject." Strauer does not teach the enrichment of any cell type from MNCs, such as by removing non-EGCs from the MNC population. While Strauer at best may teach the isolation of MNCs from crude bone marrow, it fails to teach the subsequent enrichment of any cell type, let alone by at least two-fold from this MNC population. Since Strauer fails to teach this element of claims 1, 54 and 57, it cannot anticipate these claim nor their dependent claims.

In addition to failing to teach or suggest all the elements of claim 1, Strauer fails to teach or suggest elements of many of the dependent claims.

Applicants request that if the Examiner should maintain the rejection over Strauer, that she specifically identify how Strauer allegedly teaches or suggest each element of any rejected dependent claim. For example, the Examiner has rejected claims 28 and 35, yet has failed to show how Strauer teaches the administration of human EGCs and MSCs in a ratio of from about 5:1 to about 1:5 as recited in claims 28 and 53.

Rejections under 35 U.S.C. § 103(a) - Ueno

Claims 1-4, 6-8, 10-17, 19-21, 23-36, 40-47, 49-57, and 62-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ueno et al., taken in view of Haynesworth, Yin et al., and Hess et al.

Since the Examiner previously rejected claims 1-4, 6-8, 11-17, 19-21, 23-28, 32-36, 40-47, and 49-57 as allegedly anticipate by Ueno, this obviousness rejection is being applied to non-anticipated claims 10, 29-31, 62 and 63.

Claims 10, 62 and 63 recite allogeneic sources of cells to be administered to the subject. The Examiner alleges that Hess teaches that that "allogenic bone marrow is a viable substitute for autologous transplant." Applicants traverse on the following grounds:

(1) As recited in the previous section, Ueno fails to teach the two-fold enrichment of EGCs from MNCs as recited in claims 1, 54 and 57. And the combination of Ueno with Haynesworth, Yin and Hess fail to correct this deficiency. Since the combination fails to teach all their elements, claims 1, 54 and 57, and their dependent claims are not rendered obvious by the references.

(2) Hess only teaches that succinylacetone may be used in allogeneic bone marrow transplants to reduce graft vs. host disease (e.g. see abstract "[t]he present invention discloses a method of controlling graft versus host disease, resulting from bone marrow transplantation by treating the host with succinylacetone"). Hess teaches that immune cells from the donor can react against the recipient: "the immunocompetent cells in the graft can recognize foreign antigens in the recipient and attack various tissues (gastrointestinal tract, skin, lymphoid organs and liver), leading to acute GVHD and a fatal outcome in some patients" (See background of the invention).

The pending claims, however, do not recite the administration of immunocompetent cells that would trigger an GVHD. The claims recite the administration of EGCs and MSCs, neither of which are immunocompetent cells. In other words, administering to the subject EGCs and MSCs would not trigger GVHD, and thus no succinylacetone would be needed. Accordingly, one skilled in the art would not have been motivated to combine Ueno and Hess to arrive at the claimed invention.

(3) Finally, even if there had been a motivation to combine the references, the cited references do not provide a reasonable expectation of success for the treatment of ischemia with allogeneic cells. The references do not provide an expectation of success that the transplanted cells would differentiate and integrate into host tissue to form blood vessels. Hess teaches a method of decreasing GVHD, but it does not teach a method of treating host versus graft disease (HVGD) or of preventing host destruction of donor cells. Thus, one skilled in the art would have expected that the allogenic cells would be rejected by the host, resulting in no amelioration of ischemia.

Rejections under 35 U.S.C. § 103(a) – Kalka

Claims 1-4, 6-8, 10-17, 19-21, 23-36, 40-47, 49-57, and 62-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Kalka et al. taken in view of Pittenger et al., Shake et al., Haynesworth, and Yin et al.

The combination of Kalka and the other references fail to teach all the claim elements of the pending claim and thus fail to render them obvious. Kalka, whether alone or in combination with the other references, teaches only the isolation of *peripheral blood* monocytes (See, *e.g.*, page 3422, column 2, 1st full paragraph:"[t]otal hPBMC were isolated from blood of human volunteers."). Independent claims 1, 54 and 57, however, recite the isolation of EGCs from *bone marrow* mononuclear cells. Furthermore, the elected species of endothelial generating cells is hemangioblasts. The combination of Kalka and the other references, by contrast, relates only to endothelial precursor cells (EPCs). (See, *e.g.* page 3423, column 2, 1st paragraph: "athymic mice...received an intracardiac injection of $5x10^5$ culture expanded EPCs.") EPCs are not hemangioblasts and thus the claims cannot be rendered obvious.

If the Examiner has found hemangioblasts to be patentable over Kalka and has extended the search to other species of EGCs (*i.e.* has expanded the search to EPCs), applicants request that the Examiner acknowledge the patentability of hemangioblasts in the next office action.

Lastly, the Examiner's assertion that Kalka teaches the sorting of cells with an anti-CD34+ antibody and their subsequent injection into mice is incorrect. Kalka shows on page 3423, column 1, the sorting of cells using various antibodies, including anti-CD34 antibodies, but the sorted cells were not injected into animals. Rather, the cells were "fixed in 1% paraformaldehyde" and used simply to quantitate the presence of various markers in the culture cells.

Rejections under 35 U.S.C. § 103(a) – Kawamoto

Claims 1-4, 6-8, 10-17, 19-21, 23-36, 40-47, 49-57, and 62-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Kawamoto et al., taken in view of Pittenger et al., Shake et al., Haynesworth, and Yin et al.

The combination of Kawamoto and the other references fail to teach all the claim elements of the pending claims and thus fail to render them obvious. Kawamoto, whether alone or on combination with the other references, teaches only the isolation of *peripheral blood* monocytes. Independent claims 1, 54 and 57, however, recite the isolation of EGCs from *bone marrow* mononuclear cells. Furthermore, the elected species of EGCs is hemangioblasts. The combination of Kawamoto and the other references, by contrast, relates only to endothelial precursor cells (EPCs). EPCs are not hemangioblasts and thus the claims cannot be rendered obvious.

If the Examiner has found hemangioblasts to be patentable over Kawamoto and has extended the search to other species of EGCs (i.e. has expanded the search to EPCs), applicants request that the Examiner acknowledge the patentability of hemangioblasts in the next office action.

CONCLUSIONS

In view of the above amendment, Applicants believe the pending application is in condition for allowance.

Applicants believe no additional fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 18-1945, under Order No. CWRU-P01-046 from which the undersigned is authorized to draw.

Dated: March 13, 2007

Respectfully submitted,

By _____

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